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Functional models for iron–bleomycin

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Abstract

A new pentadentate ligand, *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine (N4Py), has been prepared. The corresponding iron(II) complex, $[N4PyFe(CH_3CN)](ClO_4)_2$, serves as a functional model for the active site of iron–bleomycin. Upon treatment with H_2O_2 the formation of a purple intermediate has been observed, which has been characterized as an iron(III)–hydroperoxide complex. This N4Py–iron–hydroperoxide system has proven to be an active oxidation catalyst.

Keywords: Hydroperoxide compounds; Nonheme iron compounds; Oxygen activation

1. Introduction

The selective oxidation of unactivated organic substrates, e.g. alkanes, is a major challenge in synthetic chemistry [1]. Nature has designed a variety of ingenious metalloproteins that are capable of performing selective oxidative transformations.

Iron containing metalloproteins are abundant and a variety of functions including electron transport, reversible oxygen binding and catalytic oxidations have been observed [2]. Recently the nonheme iron enzymes capable of oxygen activation have attracted considerable attention [3]. Examples of this class include the well known dinuclear systems hemerythrin, an oxygen carrier, and methane monooxygenase, which can selectively oxidize methane to methanol [4].

A very intriguing system is that of iron–bleomycin (BLM) (Fig. 1). Iron–bleomycin is a metalloglycopeptide which is clinically used as an anticancer antibiotic [3]. In the presence of dioxygen BLM is capable of selective oxidative DNA cleavage.

The metal binding domain of BLM contains one iron(II) center, with five of the coordination sites occupied by nitrogen donor ligands. Fe(II) BLM is a high spin iron(II) complex with a sixth coordination site available for dioxygen

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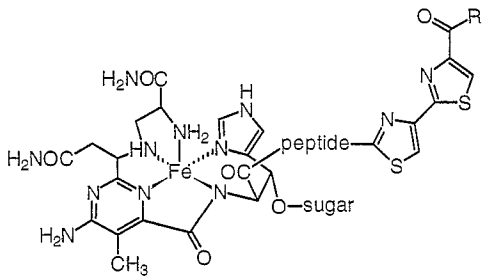


Fig. 1. Schematic representation of iron–bleomycin.

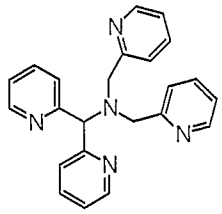


Fig. 2. The new pentadentate ligand, N4Py.

binding to form 'activated BLM'. Upon O_2 binding the ferrous complex is converted into a low spin iron(III) complex [5]. Extensive spectroscopic investigation of the oxygenated form of Fe BLM lead to the formulation of activated BLM as an iron(III) hydroperoxide complex. Besides its DNA strand scission capability, BLM is also capable of oxygenating a wide variety of organic substrates [6].

This feature makes model systems of activated BLM highly attractive in the design of new selective oxidation catalysts. In view of our longstanding interest in mimicking the active sites of oxygenase proteins [7,8], the iron–bleomycin system appealed to us, encouraged by the fact that a synthetic model system for activated BLM has been shown to mimic its DNA cleavage ability [9].

Our efforts are directed towards developing a good functional model for BLM with an emphasis on the development of a robust oxidation catalyst. This implies a synthetically simple metal–ligand system with structural features resembling iron–bleomycin retaining high oxygenation activity.

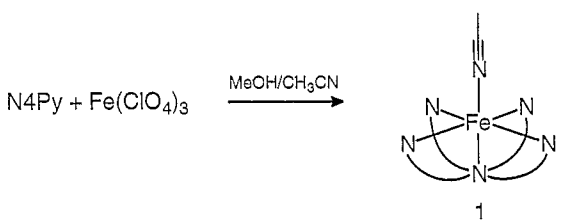
2. A synthetic model for iron–bleomycin

Based on the chemistry developed around tris(2-pyridylmethyl)amine (TPA) [7] and the structure of Fe BLM (i.e., 5 N donor set) a new pentadentate ligand, *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine (N4Py) (Fig. 2), was designed [10] to mimic the all nitrogen ligand environment of the iron center in Fe BLM. The ligand consists of one central tertiary amine group surrounded by 4 pyridyl arms. N4Py is readily obtained in a simple two step synthesis, involving coupling of 2-picolyl chloride to bis(2-pyridyl)methylamine.

Complexation of N4Py with $Fe(ClO_4)_3$ in a methanol/acetonitrile mixture gave the corresponding complex **1** as a crystalline solid in high yield (Scheme 1). This complex can be formulated as $[N4PyFe(CH_3CN)](ClO_4)_2$. The X-ray structure (Fig. 3) shows a six coordinate iron(II) center. The four pyridine N atoms are in the equatorial plane, with all the pyridine rings perpendicular to this plane. Compared to metalloporphyrin systems where the pyrrole rings are within the basal plane this binding situation is distinctly different. The apical positions are occupied by the N atom from the tertiary amine and that of an acetonitrile. From the short Fe–N bond lengths of 1.91–1.96 Å it can be deduced that the complex is in the low spin iron(II) form [11].

Further evidence for this assignment is the fact that the complex is EPR silent and exhibits a diamagnetic ^{1}H-NMR spectrum.

Cyclic voltammetry of the complex shows a reversible oxidation at 0.99 V versus saturated



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Scheme 1. Complexation of N4Py with $Fe(ClO_4)_3$.

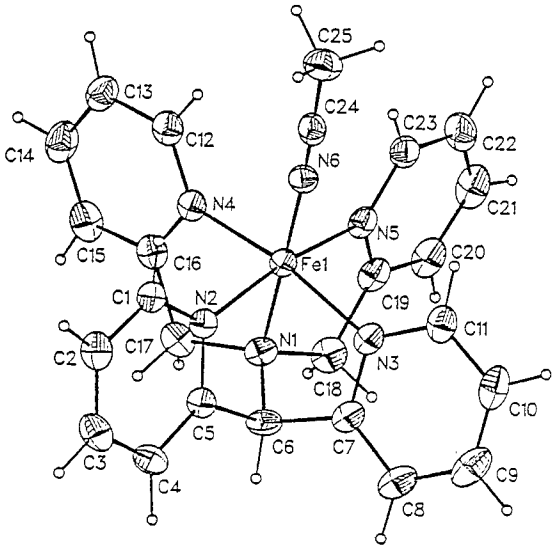


Fig. 3. Structure of the cation of **1**.

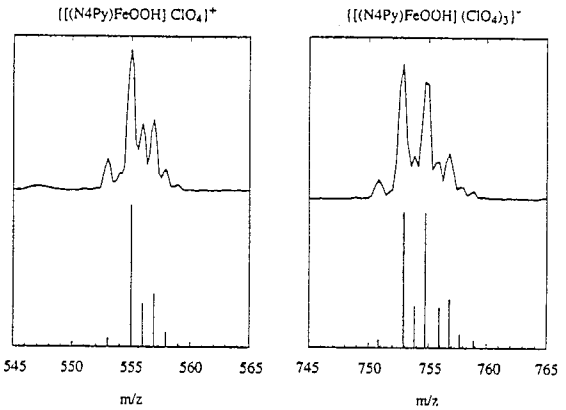
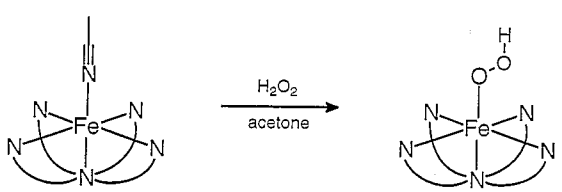


Fig. 4. Electron ionization mass spectrometric features of **2** at m/z +555 and -753; calculated isotope patterns are represented by bars under each peak cluster.

calomel electrode (SCE) corresponding to the Fe^{II}/Fe^{III} couple. This relatively high value supports the thermodynamic stability of the iron(II) state of the complex, i.e. starting with an iron(III) salt a reduction takes place during synthesis resulting in the corresponding iron(II) complex.

3. Reaction with H_2O_2

Treatment of complex **1** (UV/Vis $\lambda_{max} = 458$ nm, $\epsilon = 4000\ M^{-1}\ cm^{-1}$) with H_2O_2 in acetone (Scheme 2) results in the appearance of a purple colored species ($\lambda_{max} = 530$ nm, $\epsilon = 1100\ M^{-1}\ cm^{-1}$). This intermediate proved to be unstable, with a half-life of about 20 min at room temperature. Disproportionation of H_2O_2 is observed at ambient temperatures but the purple intermediate can be regenerated by addition of aqueous H_2O_2. The purple intermediate exhibits an EPR spectrum with g values 2.17, 2.12 and 1.98, indicative of a low spin iron(III) species. On the basis of these g values, which resemble those of activated BLM, an iron(III) hydroperoxide structure (**2**) was proposed [9].



1 2

Scheme 2. Reaction of **1** with H_2O_2.

This formulation was confirmed using electrospray ionization mass spectrometry. In the positive ion spectrum the most prominent peak was found at $m/z = 555$, corresponding to $\{[(N4Py)FeOOH]ClO_4\}^+$. In the negative ion spectrum the most prominent peak was observed at $m/z = 753$, which corresponds to $\{[(N4Py)FeOOH](ClO_4)_3\}^-$.

Furthermore, the observed isotope intensity patterns match those of the calculated patterns for their formulae, thus supporting the iron(III) hydroperoxide structure (Fig. 4).

Based on the available coordination site in **1**, occupied by the labile acetonitrile ligand, an end-on coordination mode of the hydroperoxide in **2** is proposed. The spectroscopic evidence for this synthetic hydroperoxo-iron(III) species also supports the activated form of BLM as $Fe^{III}(BLM)OOH^+$ [9] [10].

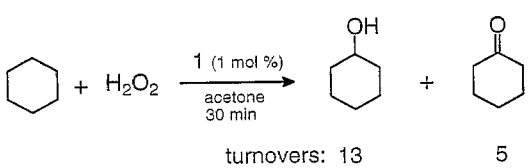
4. Catalytic oxidation

The N4PyFe^{II} complex in the presence of hydrogen peroxide (presumably involving the $[(N4Py)FeOOH]^{2+}$ species) proved to be a very active oxidation catalyst. An example is the catalytic oxidation of cyclohexane (Scheme 3).

Treatment of **1** with 100 equivalents H_2O_2 in the presence of 1000 equivalents cyclohexane in acetone gave after 30 min reaction time 13 equivalents cyclohexanol and 5 equivalents cyclohexanone with respect to complex **1**. This activity is comparable to those observed for Fe(tpa) [12] and $Fe(bpy)_2$ (bpy = 2,2′-bipyridine) [13] complexes and the 'Gif' family of catalysts [14]. The involvement of the hydroperoxo complex **2** in the catalytic cycle, either as catalyst or as precursor to the actual catalyst, is supported by the observation that oxidation ceases upon disappearance of the purple color. Complex **1**, in the presence of H_2O_2, compares favorably to the best nonheme iron oxidation catalysts reported thus far.

5. Conclusions

$N4PyFe(CH_3CN)(ClO_4)_2$ has proven to be an attractive functional model for iron–bleomycin although the N4Py ligand is completely different from the natural systems. Upon treatment with H_2O_2 a purple intermediate is formed which could be characterized as an iron(III) hydroperoxide complex, $[(N4Py)FeOOH]^{2+}$. Preliminary experiments indicate that this iron hydroperoxide complex is among the most powerful nonheme iron oxidation catalysts known to date.



Scheme 3. Catalytic oxidation of cyclohexane with H_2O_2 using **1** as a catalyst.

6. Experimental section

6.1. Synthesis of N4Py

2-Picolyl chloride hydrochloride (6.8 g, 41.5 mmol) was added to an aqueous solution of NaOH (5 M, 8.3 ml) at 0°C. After stirring for 10 min, this solution was added to bis(2-pyridyl)methylamine (4.13 g, 20.75 mmol) and another portion of aqueous NaOH (5M, 8.3 ml) was added. After stirring for 48 h at 25°C, concentrated $HClO_4$ was added to precipitate a yellow solid, which was recrystallized from hot water. Treatment of this perchlorate salt with 2.5 M NaOH solution and extraction with dichloromethane yielded the free amine of N4Py (2.84 g, 37% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 3.97$ (s, 4H, CH_2), 5.35 (s, 1 H, CH), 7.13 (m, 4H, Py), 7.63 (m, 8 H, Py), 8.51 (d, 2H, $J = 4.8$ Hz, Py), 8.57 (d, 2H, $J = 4.8$ Hz, Py).

6.2. Synthesis of $N4PyFe(CH_3CN)(ClO_4)_2$

To a solution of N4Py (0.144 g, 0.392 mmol) in methanol/acetonitrile (2 ml/2 ml) was added $Fe(ClO_4)_3 \cdot 10H_2O$ (0.215 g, 0.403 mmol). After stirring for 5 min, the solution was placed in an ethylacetate bath. The red crystalline product was collected and washed with ethylacetate to yield **1** as dark, red crystals (0.178 g, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 4.27$ (d, 2H, $J = 18.1$ Hz, CH_2), 4.40 (d, 2H, $J = 18.1$ Hz, CH_2), 6.34 (s, 1H, CH), 7.06 (d, 2H, $J = 7.8$ Hz, Py), 7.33 (m, 4H, Py), 7.68 (m, 2H, Py), 7.88 (m, 4H, Py), 8.90 (d, 2H, $J = 5.4$ Hz, Py), 9.03 (d, 2H, $J = 5.4$ Hz, Py); UV/Vis (acetone): λ_{max} (ϵ) = 382 (5700), 458 (4000); anal. calcd. for $C_{25}H_{28}Cl_2FeN_6O_{10}$: C 42.94, H 4.04, N 12.02; found: C 43.21, H 3.76, N 12.02.

Acknowledgements

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